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Complications - Infection

Tranexamic Acid Is Associated With Reduced Periprosthetic Joint Infection After Primary Total Joint Arthroplasty

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ABSTRACT

Background: Previous studies have demonstrated preoperative anemia to be a strong risk factor for periprosthetic joint infection (PJI) in total joint arthroplasty (TJA). Allogeneic blood transfusion can be associated with increased risk of PJI after primary and revision TJA. Tranexamic acid (TXA) is known to reduce blood loss and the need for allogeneic blood transfusion after TJA. The hypothesis of this study is that administration of intravenous TXA would result in a reduction in PJI after TJA.
Methods: An institutional database was utilized to identify 6340 patients undergoing primary TJA between January 1, 2013 and June 31, 2017 with a minimum of 1-year follow-up. Patients were divided into 2 groups based on whether they received intravenous TXA prior to TJA or not. Patients who developed PJI were identified. All PJI patients met the 2018 International Consensus Meeting definition for PJI. A multivariate regression analysis was performed to identify variables independently associated with PJI.
Results: Of the patients included, 3683 (58.1%) received TXA and 2657 (41.9%) did not. The overall incidence of preoperative anemia was 16%, postoperative blood transfusion 1.8%, and PJI 2.4%. Bivariate analysis showed that patients who received TXA were significantly at lower odds of infection. After adjusting for all confounding variables, multivariate regression analysis showed that TXA is associated with reduced PJI after primary TJA.
Conclusion: TXA can help reduce the rate of PJI after primary TJA. This protective effect is likely interlinked to reduction in blood loss, lower need for allogeneic blood transfusion, and issues related to immunomodulation associated with blood transfusion.

Periprosthetic joint infection (PJI) is a rare, yet a devastating, complication of total joint arthroplasty (TJA). It occurs in 1%-2% of TJA procedures [1–3] and is one of the most common reasons for TJA revision [4–10].

By 2030, primary TJA has been projected to grow by 174% to 572,000 for primary total hip arthroplasty (THA) and by 673% to 3.48 million for primary total knee arthroplasty (TKA) [11]. Failures of TJA because of complications such as infection, loosening, periprosthetic fracture, and postoperative pain are indications for revision surgery [12]. These revisions will become a tremendous burden to the health systems, with a projected estimate cost of $13 billion in 2030 [12]. Given the increased demands for arthroplasty, patients should be perioperatively optimized to minimize the incidence of PJI, and other complications, following TJA.

Preoperative anemia and blood loss during primary TJA leading to allogeneic blood transfusion have been identified as risk factors for surgical site infection (SSI) and PJI in TJA [13–16]. This has led to a growing increase in the use of antifibrinolytic drugs to reduce blood loss and blood transfusion post TJA [17]. The results from previous studies and extensive meta-analysis have established that tranexamic acid (TXA) is a safe and effective drug for reducing

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blood loss and the need for allogeneic blood transfusion post-TJA [17–19].

Although efficacy of TXA in reducing blood loss and the need for allogeneic blood transfusion has been well established, the potential role of TXA in reducing PJI following TJA has not been elucidated. This study was conceived to examine the hypothesis that administration of intravenous (IV) TXA can lead to a reduction in PJI after primary TJA.

Materials and Methods

Following Institutional Review Board approval, a prospectively maintained, single-institution database was queried to identify 7725 patients undergoing primary TJA between January 1, 2013 and June 31, 2017. All patients who had primary THA or TKA were included. For patients who had multiple joints replacement, each joint was considered as a separate case. Patients undergoing revision arthroplasty, primary arthroplasty in tumor cases, and those with inadequate follow-up (1012) were excluded (Fig. 1).

Overall, 6340 cases were included in the study with minimum 1-year follow-up. Of these, 2927 (46.2%) were male. The mean age was 64.72 ± 10.7 years (range 12-98) and the mean body mass index (BMI) was 29.8 ± 5.3 kg/m^2 (range 14-58.3) (Table 1). The mean follow-up was 26.3 months (range 12-67.3).

The cohort was divided into 2 groups: patients who received IV TXA prior to arthroplasty (3683 patients) and those who did not receive TXA (2657 patients). Patients in the TXA group were all administered a single dose of TXA (15 mg/kg) intravenously, 20-30 minutes prior to incision or inflation of tourniquet. The antibiotic and postoperative care was the same for both patient groups. The majority of patients (91.8%) in the study received aspirin (325 mg/d or 81 mg bid) for 4 weeks postoperatively. Using the World Health Organization definition, preoperative anemia was defined as hemoglobin (Hgb) <13 g/dL in males and Hgb <12 g/dL in females. Patient demographics, comorbidities, operative details, and perioperative variables were recorded and compared across the 2 cohorts.

Patients who developed PJI following primary TJA were identified using the 2018 International Consensus Meeting definition [20] and subsequently confirmed by manual chart review.

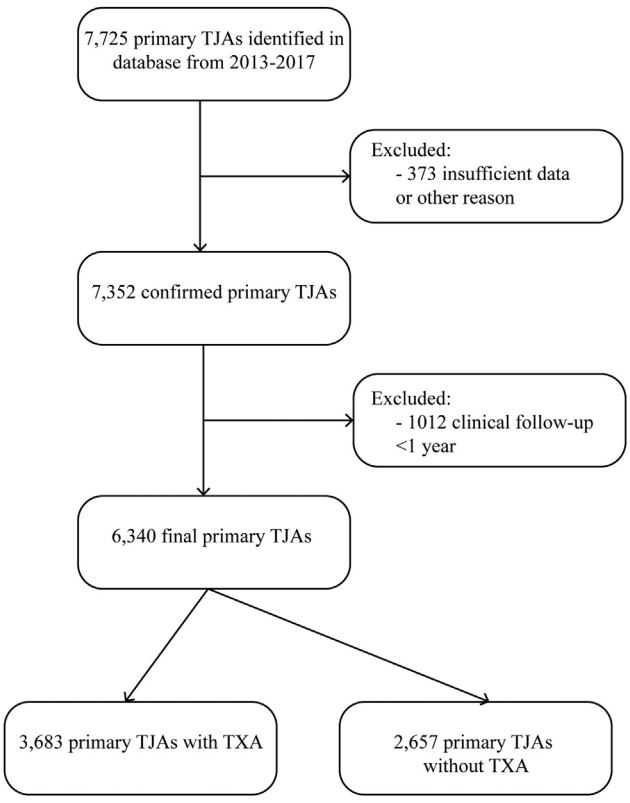

Fig. 1. Flow diagram detailing patient inclusion, exclusion, and grouping. TJA, total joint arthroplasty; TXA, tranexamic acid.

Table 1
Patient Demographics.

Gender (%)	
Male	2927 (46.2)
Female	3413 (53.8)
Age (y), mean ± SD (range)	64.72 ± 10.7 (12-98)
Race (%)	
Caucasian	4753 (75)
African American	1048 (16.5)
Hispanics	77 (1.2)
Asians	35 (1.2)
Others	387 (6.1)
BMI (kg/m^2), mean ± SD (range)	29.8 ± 5.3 (14-58.3)
Type of surgery (%)	
TKA	3028 (47.8)
THA	3312 (52.2)
TXA (%)	
Yes	3683 (58.1)
No	2657 (41.9)
Anemic (%)	
Yes	971 (16)
No	5090 (84)

SD, standard deviation; BMI, body mass index; TKA, total knee arthroplasty; THA, total hip arthroplasty; TXA, tranexamic acid.

Statistical Analyses

The 2 groups (TXA vs no TXA) were compared on categorical variables with Fisher's exact tests and on continuous variables with *t*-tests for independent groups or Mann-Whitney *U* for nonparametric variants. Preliminary bivariate logistic regression analyses were conducted to determine whether various preoperative and patient variables were significantly related to PJI outcomes. Variables which were related to PJI in the bivariate analyses ($P < .25$ as recommended by Hosmer and Lemeshow, 2000) were considered for logistic regression model. All analyses were conducted with the statistical packages SPSS (IBM Corp, 2013, version 23, Armonk, NY).

Results

Overall, 3683 patients (58.1%) received IV preoperative TXA. The overall incidence of preoperative anemia was 16%, postoperative blood transfusion was 1.8%, and PJI rate was 2.4%. Most of TJA surgeries were done under neuraxial anesthesia (91.7%) and nearly all (96.6%) of total knee replacements were done under tourniquet.

The preliminary analyses showed that patients receiving TXA were younger, more likely to be female, had a lower BMI and comorbidities, and undergoing THA. This group was also more likely to receive aspirin (for deep vein thrombosis [DVT] prophylaxis) and had less anemia (all $P < .05$; Table 2). The outcome measurement showed that the TXA group has a smaller postoperative Hgb decrease, less need for allogeneic blood transfusion, shorter length of hospitalization, less wound complications, and lower PJI rate (all $P < .05$; Table 3). Intraoperative blood loss, 90-day readmission, and postoperative thromboembolic events were similar in both groups.

With regard to PJI rate, bivariate analyses (Table 4) showed that rheumatoid arthritis (odd ratio [OR] 5.07, 95% confidence interval

Table 2
Univariate Analysis.

Variables	Total (n = 6340)	Non-TXA (n = 2657)	TXA (n = 3683)	*P*-Value
Age (y), mean ± SD	64.7 ± 10.7	66.9 ± 10.5	63.1 ± 10.5	<.001
Gender, female (%)	3413 (53.8)	1306 (49.2)	2107 (57.2)	<.001
BMI (kg/m^2), mean ± SD	29.8 ± 5.3	30.0 ± 5.3	29.7 ± 5.3	.012
Race, Caucasian (%)	4753 (75.0)	1912 (72.0)	2841 (77.1%)	<.001
Joint, knee (%)	3028 (47.8)	1369 (51.5)	1659 (45.0)	<.001
CCI, mean ± SD	0.5 ± 1.0	0.8 ± 1.2	0.4 ± 0.8	<.001
CCI ≥ 1 (%)	2034 (32.1)	1111 (41.8)	923 (25.1)	<.001
Diabetes (%)	379 (6.0)	190 (7.2)	189 (5.1)	<.001
Malignancy (%)	68 (1.1)	37 (1.4)	31 (0.8)	.036
Renal disease (%)	188 (3.0)	140 (5.3)	48 (1.3)	<.001
Liver disease (%)	49 (0.8)	24 (0.9)	25 (0.7)	.314
Rheumatic arthritis (%)	284 (4.5)	140 (5.3)	144 (3.9)	.01
Preoperative hemoglobin (g/L), mean ± SD	13.3 ± 1.6	13.1 ± 1.8	13.5 ± 1.5	<.001
Anemia (%)	971 (16.0)	510 (20.9)	461 (12.7)	<.001
Coagulopathy (%)	106 (1.7)	81 (3.1)	25 (0.7)	<.001
Simultaneous bilateral TJA (%)	336 (5.3)	80 (3.0)	256 (7.0)	<.001
Neuraxial anesthesia (%)	5812 (91.7)	2365 (89.2)	3447 (93.6)	<.001
Tourniquet (%)	2925 (96.6)	1322 (96.6)	1603 (96.6)	.93
Anticoagulation				<.001
Aspirin (%)	5813 (91.8)	2304 (87.0)	3509 (95.3)	
Warfarin (%)	330 (5.2)	255 (9.6)	75 (2.0)	
Others	188 (3.0)	89 (3.4)	99 (2.7)	
Intraoperative antibiotics				.601
Cephalosporin (%)	5224 (82.5)	2182 (82.5)	3042 (82.6)	
Vancomycin (%)	1082 (17.1)	452 (17.1)	630 (17.1)	
Others (%)	23 (0.4)	12 (0.5)	11 (0.3)	
Operative time (min), mean ± SD	101.5 ± 39.8	102.5 ± 40.5	100.9 ± 39.3	.111

TXA, tranexamic acid; SD, standard deviation; BMI, body mass index; CCI, Charlson comorbidity index; TJA, total joint arthroplasty.

[CI] 3.28-7.83, $P = .000$), higher BMI (OR 1.06, 95% CI 1.03-1.09, $P = .000$), higher Charlson Comorbidity Index (OR 1.27, 95% CI 1.13-1.43, $P = .000$), male gender (OR 1.58, 95% CI 1.14-2.20, $P = .005$), renal disease (OR 3.86, 95% CI 2.22-6.73, $P = .000$), liver disease (OR 3.74, 95% CI 1.33-10.54, $P = .01$), coagulopathies (OR 2.54, 95% CI 1.09-5.88, $P = .03$), longer length of hospital stay (OR 1.18, 95% CI 1.13-1.23, $P = .000$), longer operation time (OR 1.01, 95% CI 1.01-1.02, $P = .000$), and anemia (OR 4.63, 95% CI 3.31-6.46, $P = .000$) were associated with higher odds of PJI. Administration of TXA (OR 0.47, 95% CI 0.34-0.66, $P = .000$), neuraxial anesthesia (OR 0.32, 95%CI 0.21-0.48, $P = .000$), and simultaneous bilateral surgeries (OR 0.24, 95% CI 0.06-0.96, $P = .04$) were associated with lower odds of infection.

After controlling for confounding variables, multivariate analysis showed that administration of TXA (OR 0.68, 95% CI 0.46-0.99, $P = .04$) was associated with lower rate of PJI. TXA also was more effective in nonanemic patients (OR 0.52, 95% CI 0.32-0.84, $P = .008$) and patients undergoing hip arthroplasty (OR 0.50, 95% CI 0.31-0.81, $P = .005$) than anemic patients and those undergoing knee arthroplasty (Table 5).

Table 3
Outcome Measurements.

Variables	Non-TXA (n = 2657)	TXA (n = 3683)	*P*-Value
IOBL (mL), mean ± SD	147.8 ± 240.3	147.7 ± 159.5	.99
Hemoglobin drop (g/L), mean ± SD	2.3 ± 1.8	2.0 ± 1.6	.000
Postoperative blood transfusion (%)	75 (2.8)	41 (1.1)	.000
Length of stay (d), mean ± SD	2.4 ± 2.5	1.8 ± 1.4	.000
Wound complication (%)	35 (1.5)	15 (0.4)	.000
DVT (%)	0 (0.0)	4 (0.1)	.16
PE (%)	5 (0.2)	2 (0.1)	.120
PJI (%)	90 (3.4)	60 (1.6)	.000
Type of PJI (%)			.68
Acute	27 (30.0)	16 (26.7)	
Chronic	62 (68.9)	42 (70.0)	
Hematogenous	1 (1.1)	2 (3.3)	
90-d readmission (%)	120 (4.5)	155 (4.2)	.55

TXA, tranexamic acid; IOBL, intraoperative blood loss; SD, standard deviation; DVT, deep vein thrombosis; PE, pulmonary embolism; PJI, periprosthetic joint infection.

Discussion

The association between preoperative anemia and SSI or PJI has been demonstrated in numerous prior studies [13–16,21–24]. Patients with preoperative anemia have higher likelihood of needing

Table 4
Bivariate Predictors of PJI via Logistic Regression.

Predictor	OR (95% CI)	*P*-Value
TXA	0.47 (0.34-0.66)	.000
Age (y)	1.00 (0.99-1.02)	.95
Male	1.58 (1.14-2.20)	.005
BMI (kg/m^2)	1.06 (1.03-1.09)	.000
Race, not Caucasians	0.71 (0.47-1.07)	.10
Knee	0.77 (0.55-1.06)	.11
CCI scores	1.27 (1.13-1.43)	.000
Diabetes	1.00 (0.51-1.99)	.99
Malignancy	1.25 (0.30-5.17)	.75
Renal disease	3.86 (2.22-6.73)	.000
Liver disease	3.74 (1.33-10.54)	.01
Rheumatic arthritis	5.07 (3.28-7.83)	.000
Anemia	4.63 (3.31-6.46)	.000
Coagulopathy	2.54 (1.09-5.88)	.03
Simultaneous bilateral TJA	0.24 (0.06-0.96)	.04
Neuraxial anesthesia	0.32 (0.21-0.48)	.000
Warfarin	2.20 (1.54-3.15)	.000
Vancomycin	2.20 (1.54-3.15)	.000
Operative time (min)	1.01 (1.01-1.02)	.000
Length of stay (d)	1.18 (1.13-1.23)	.000

PJI, periprosthetic joint infection; OR, odds ratio; CI, confidence interval; TXA, tranexamic acid; BMI, body mass index; CCI, Charlson comorbidity index; TJA, total joint arthroplasty.

Table 5
Multivariate Analysis for Association Between TXA and PJI.

Variables	PJI Rate	Nonadjusted OR (95% CI)	*P*-Value	Adjust OR (95% CI)	*P*-Value
Overall					
Without TXA	3.4%	Reference		Reference	
With TXA	1.6%	0.47 (0.34-0.66)	<.001	0.68 (0.46-0.99)	.045
With anemia					
Without TXA	7.8%	Reference		Reference	
With TXA	5.6%	0.70 (0.42-1.17)	.175	1.14 (0.60-2.17)	.683
No anemia					
Without TXA	2.3%	Reference		Reference	
With TXA	1.1%	0.46 (0.29-0.71)	.001	0.52 (0.32-0.84)	.008
Hip					
Without TXA	4.2%	Reference		Reference	
With TXA	1.7%	0.39 (0.25-0.60)	<.001	0.50 (0.31-0.81)	.005
Knee					
Without TXA	2.6%	Reference		Reference	
With TXA	1.6%	0.59 (0.35-0.98)	.042	1.18 (0.63-2.23)	.600

TXA, tranexamic acid; PJI, periprosthetic joint infection; OR, odds ratio; CI, confidence interval.

allogeneic blood transfusions and are at higher risk of developing PJI [13–16]. Thus, strategies to optimize anemic patients preoperatively and minimize blood loss during surgery have been implemented to reduce the need for allogeneic blood transfusion [25]. One such strategy has been the administration of TXA during TJA with proven efficacy to reduce blood loss and the need for allogeneic blood transfusion [17–19,26–30]. The current study corroborates the findings of prior studies by demonstrating an excellent efficacy for TXA. Patients in the current study who received TXA had less Hgb drop postoperatively and were less likely to require blood transfusion and had lower rate of postoperative wound complications. This group also had shorter length of hospital stay and lower rate of PJI.

A recent study demonstrated additional benefits to TXA when administered to patients undergoing TKA [31]. Patients receiving TXA had less hidden blood loss, a lower ratio of postoperative knee swelling, less postoperative knee pain, lower levels of inflammatory biomarkers, better early knee function, and better satisfaction than those treated with tourniquet alone [32]. Administration of TXA is also safe with no real concerns that can be gleaned from the literature. TXA has also been exonerated from causing venous thromboembolism (VTE). A recently published meta-analysis concluded that administration of topical, IV, and oral TXA was not associated with an increased risk of VTE [33]. We also found no differences between both groups in terms of DVT, pulmonary embolism, and 90-day readmissions.

Most of the patients who received TXA were also placed on aspirin for VTE prophylaxis. Heller et al [34] have demonstrated that TXA can be used along with aspirin safely in arthroplasty patients without increasing the risk of subsequent VTE. Our results also showed that this combination did not affect the rate of DVT, pulmonary embolism, and readmissions. In addition, a study by Kim et al [35] detected that administration of intra-articular TXA resulted in fewer wound complications compared to patients who did not receive TXA. We also observed a similar finding.

The confounding variable that influences blood loss during TKA is the issue of tourniquet. Alcelik et al [36] in a systemic review concluded that the total and intraoperative blood loss was less when a tourniquet was used. On the other hand, Yi et al [37] published a meta-analysis demonstrating that the use of tourniquet during TKA resulted in a higher rate of PJI. In our cohort, most of the knee surgeries (96.6%) were done with the use of tourniquet and both groups were similar in terms of tourniquet use. We are not able to study the influence of tourniquet on blood loss and examine its potential confounding effect. The other confounding variable relates to the type of anesthesia used during TJA. Studies comparing neuraxial anesthesia with general anesthesia during TJA have reported conflicting observations. But the overwhelming majority of studies demonstrate that the use of hypotensive neuraxial anesthesia leads to a lower blood loss, lower rate of SSI, wound complications, and fewer overall complications than those receiving general anesthesia [38–40]. Our results also confirmed previous studies.

Bivariate analysis has shown that in addition to TXA, other variables such as male gender, BMI, Charlson Comorbidity Index, rheumatoid arthritis, renal disease, liver disease, coagulopathy, anemia, operation time, and length of stay affect the PJI rate after primary TJA which is supported by the literature [2,3,13,15,21,23,41–44]. After adjusting for all variables related to outcomes, TXA was an independent risk factor protecting against PJI. The protective effect of TXA was more in hip joints and nonanemic patients.

The unadjusted and adjusted models predicting PJI may be affected by variations in patients with or without TXA. Patients who did not receive TXA in the current study tended to be male, older, sicker, anemic, higher BMI, and less likely to receive aspirin for DVT prophylaxis or neuraxial anesthesia. These reasons for not receiving TXA were due to previous traditional contraindications of TXA in our hospital. These variables are also predisposing factors for increased PJI. Based on recent studies on the safety of TXA, the indications for TXA are increasing even in sicker patients [33,35,45,46]. In an effort to remove the influence of these variables, we did perform a regression analysis to identify the influence of TXA administration alone on the incidence of PJI. The regression analysis revealed that TXA is associated with reduced PJI after primary TJA.

This study does have several strengths. First, we extracted data from the clinical charts of all these patients that resulted in obtaining more accurate data than relying on administrative data. Second, all patients at our institution are followed closely for the first 90 days by nurse navigators. Thus, it is unlikely that any complications or readmissions in these patients, even when presented to an outside facility, were missed. Third, we attempted to study the influence of various risk factors on PJI and adjust for these confounding variables in the statistical analyses. Finally, we used a strict definition for PJI removing subjective evaluations to define PJI.

This study also has some limitations. First, it is a retrospective study with all possible biases that such study design introduces. In our hospital, TXA has been used since 2012. Initially, it was administrated in small groups of healthier patients. In 2013-2014, the indications for TXA were expanded gradually and we had more patients who received TXA. Recently, almost all TJAs are done with the administration of TXA. To have more patients with enough follow-ups and less time-dependent confounding factors, we selected all primary TJAs from January 1, 2013 to June 31, 2017. This restricted the number of cases and probably affected our results in the multivariate model for anemic patients. Second, this study was not performed

using matching criteria. We attempted to perform matching based on strict criteria, but even in case of one-by-one matching, a high attrition was observed. Third, this study was completed at an urban, tertiary referral center that does a high volume of primary TJA, and results may not be generalizable to all centers.

Conclusion

Based on the findings of this study, TXA appears to be associated with reduced PJI following primary TJA. Although the exact reason for such finding is unknown, we speculate that the beneficial effect on TXA may relate to its efficacy in reducing blood loss and the need for allogeneic blood transfusion, both of which are known to influence SSI after all surgical procedures including TJA.

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